DETAILED ACTION

Status of Application

1. Claims 1-26 are presented for examination on the merits. The following objections and rejections are made.

Instantly Claimed Subject Matter

2. A pharmaceutical composition and a method for making the composition wherein the composition is in the form of a soft gelatin capsule resistant to gastric juice and soluble in the intestine and is useful for the treatment of duodenal ulcers and other related ailments. The composition comprises a gelatin shell resistant to gastric juice and soluble in intestine having an enteric polymer such as hydroxypropyl methyl cellulose used at a weight percent of 5.0 and 25.0% mixed with gelatin in the form of free acid or its salt. The capsule incorporates a enantiomers of omeprazole such as esomeprazole, rabeprazole or its salts or its derivatives or their mixtures, a hydrophobic oily substance (such as corn oil) or a mixture of such oily substances which is used at a weight percentage of 35.0 to 90.0%, an alkaline inert reacting material such as salts of phosphoric acid, a suspending agent such as silicon dioxide which is used at a weight percentage of 1.0 to about 10.0%, a surface active agent and/or a solublising agent such as Cremophor EL which is used at weight percentage of 4.0 to 15.0%; wherein the resulting capsules being insoluble in aqueous medium up to a pH of 5.5 but quickly dissolving above pH of 6.0.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. **Claims 1-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

5. Regarding claims 1-13, 16, 19, 21, 23, and 25 the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

6. Regarding claims 3-7, 10-13, 16-18 and 23-26, the phrase "and the like" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "and the like"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

7. Claims 1-26 are vague and indefinite in that the metes and bounds of the term 'derivative' is unclear. It is unclear what is meant from these terms. Esomeprazole could be subjected to hydrogen iodide which would convert the -OMe ether linkages to –OH, as well as create the byproduct methyl iodide. Technically, methyl iodide would lead to such a derivative due to the departure of the methyl group. Thus, the metes and bound of "derivative" would be unclear to a person of ordinary skill in the art.

8. Additionally, in claim 1 (and claim 14) the claim is unclear as it recites, "a composition comprising enantiomers of omeprazole such as esomeprazole, rabeprazole or its salts..." But since rabeprazole does not have the same molecular structure or an identical empirical formula as that of omeprazole, it is unclear how one is an enantiomer of the other. Clarification is required.

9. Claim 11, dependent upon claim 1, and claim 24, dependent upon claim 14, recites the limitation, "wherein the amount ranging from 5.0 to 40.0 percent, preferably 10.0 to 25.0 percent

by weight, with reference to the contents filled in capsule". However, claim 1 (and claim 14) is quite broad and claim 11 (and 24) fails to limit or define what the weight percentages are specifically directed to. Clarification is required.

10. Claims 5, 7, 9, 18, 20 and 22 are rejected because the claims provide a narrower range within a claim that already specifies a specific range. For example, in claim 5, it is recited, "the amount employed ranging from 2.0 to 40.0%, preferably 5.0 to 25.0% by weight". It is unclear which range dominates the claim and whether or not the claimed narrower range is a limitation. This rejection may be overcome by putting the narrower range in proper dependent form. Appropriate correction is required.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. **Claims 1-10 and 12-26 rejected under 35 U.S.C. 103(a) as being unpatentable over Venkateswara et al. (WO 01/24780; IDS reference) in view of Phillips (US 2002/0045646).**

14. The teaching of Venkateswara et al. ('780) is drawn to a benzimidazole derivative containing soft gel capsule formulated for the treatment of duodenal ulcers wherein the capsule is resistant to digestive juices present in the stomach. Benzimidazole derivatives exemplified by '780 include compounds such as omeprazole which is a known proton pump inhibitor meaning that it inhibits the secretion of excess gastric juices.

15. The formulation of'780 consists of a gelatin shell and a capsule therein which consists of a composition comprising a benzimidazole derivative, a hydrophobic oily substance, an alkaline inert reacting material, a suspending agent and a surface active agent and/or solubilizing agent. It is also a requirement of '780 that the capsule is insoluble in aqueous medium up to a pH of 5.5 by is soluble so long as the pH of the medium is greater than 6.0 (see claim 1). The enteric polymers required for the composition of '780 include hydroxylpropyl methyl cellulose which is employed at a weight percentage of 5.0 to 25.0 (see claim 3). The oily substance required by '780 includes vegetable oils from different origins such as sesame oil, corn oil and soybean oil ranging from 50.0 to 80.0% by weight (see claim 4). The dispersing agents used include silicon dioxide and polyvinylprrolidone (also known as povidone) at a weight percentage ranging from 1.0 to 10.0%. The surface active agent and/or a solubilizing agents implemented by '780 include Cremophor EL ranging from 5.0 to 15.0% by weight (see claim 5). The alkaline inert reacting materials include aluminum and sodium salts of phosphoric acid ranging from 10.0 to 25.0 % by weight (see claim 6). The soft gel capsules of '780 are treated with a gelatin cross-linking agents

such as formaldehyde and the capsules are treated with dilute solutions of acids such as hydrochloric and nitric acid (see claims 7 and 8).

16. The process for preparing a pharmaceutical composition as described above is also present in claim 9 of reference '780. It should be noted that claim 9 of '780 is substantially the same as claim 14 of the instant application. Furthermore, various methods for preparing soft gel capsules containing a benzimidazole are taught in Examples 1-10. For example, Example 10 of '780 teaches that the gelatin shell consists of gelatin (40% wt.), triethyl citrate (7.5% wt.), glycerin (10.0% wt.), water (20.0% wt.), methacrylic acid copolymer type-A (7.5%), and ammonia solution (17.5%). The medicament composition includes soybean oil (80.0 % wt.), omeprazole (5.7% wt.), meglumine (5.7% wt.), and colloidal silicon dioxide (8.5% wt.). Example 10 also includes steps illustrating how the capsule is to be manufactured. The soft gel capsules may be treated with a cross-linking agent to make the capsule insoluble in gastric juices. The treatment may be done by either coating 0.05 to 1.0% w/v of the substance in an alcohol containing aqueous solution on to the soft gel or mixing cross-linking agents in the gelatin mass before capsule manufacture. Cross-linking agents exemplified include formaldehyde and glutaraldehyde (see page 6, lines 18-29). It is also taught by '780 that dilute acids such as hydrochloric and nitric acid are used to neutralize excess alkali metal salts used in the formulation (see page 6, lines 8-17).

17. However, '780 fails to teach the use of the benzimidazole compounds esomeprazole and rabeprazole.

18. The teaching of Phillips ('646) cures this deficiency. '646 is drawn to a delayed release compositions for treating gastric acid disorders, specifically the inhibition of gastric acid

secretion by H^+, K^+-ATPase enzyme system at the secretory surface of the gastric parietal cells (see [0003]), by employing pharmaceutical composition comprising a proton pump inhibitor to inhibit said enzyme system. It is taught by '646 that proton pump inhibitors are prescribed for the short-term treatment of active duodenal and gastric ulcers (see [0004]). The term proton pump inhibitor includes any substituted benzimidazole possessing pharmacological activity as an inhibitor of H^+, K^+-ATPase including rabeprazole and esomeprazole, as well as omeprazole (see [0054] and claim 1).

19. Thus, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to have combined the teachings of '780 with '646 because in doing so one would create a delayed release capsule containing esomeprazole and rabeprazole effective for the treatment of duodenal ulcers. The significance of '780 is that it teaches a composition and a method of making a soft gel capsule containing a benzimidazole derivative, a hydrophobic oily substance, an alkaline inert reacting material, a suspending agent and a surface active agent and/or solublizing agent. '780s' claim 1 appears to be a substantial duplicate of claim 1 of the instant application except for the limitation regarding the specific class of compound being used in the capsule. The compounds recited in 780 are drawn to benzimidazole derivatives whereas the instant application is drawn to enatiomers of omeprazole (i.e. esomeprazole) and rabeprazole. Albeit the compounds between the two are different, they both belong to the same family of pharmaceutical compounds which are potent inhibitors of gastric H^+, K^+-ATPase activity. The disclosure of '646 reinforces this notion as it teaches that esomeprazole and rabeprazole possess such inhibitory activity. Therefore, their use in the instantly claimed composition and method of making the composition would be obvious. With regard to the process of making the gel capsule,

this too is obvious. Claim 9 of '780 is essentially identical to claim 14 of the instant application except for the recitation of the specific active species added to the formulation (i.e. benzimidazole vs. esomeprazole and rabeprazole). Again, this deficiency is cured by the functional equivalence of the species as discussed above. Additionally, with regard to the process of making the composition, a person of ordinary skill in the art would readily vary the amounts of oily substance, alkaline inert reacting material, etc. in order to determine the optimum amount of each so the their final product would possess the greatest stability in the stomach and therapeutic efficacy. As both references used in this rejection are within the same general field of endeavor (i.e. pH dependent release of benzimidazole compounds for treatment of duodenal ulcers), it would have been obvious to one of skill in the art to combine them and arrive at a final product and method of making the product possessing the properties instantly claimed. Therefore, it would have been obvious to one ordinarily skilled in the art to combine the teachings of '780 with '646 with a reasonable expectation of success.

Conclusion

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kyle A. Purdy whose telephone number is 571-270-3504. The examiner can normally be reached from 9AM to 5PM.

21. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Ardin Marschel and Cecilia Tsang, can be reached on 571-272-0718 or 571-272-0562, respectively. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Kyle A. Purdy/
Examiner, Art Unit 4173

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614